PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VS:CE:FP16839	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU02/01427**	International Filing Date *(day/month/year)* 17 October 2002	Priority Date *(day/month/year)* 17 October 2001
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07K 7/56; A61K 38/08; A61P 11/00, 9/10, 17/00, 37/00		
Applicant UNIVERSITY OF QUEENSLAND et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **5** sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand 16 May 2003	Date of completion of the report 25 November 2003
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **O.L. CHAI** Telephone No. (02) 6283 2482

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU02/01427

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-38, 40-41, 43-72, 80** as originally filed,
pages , filed with the demand,
pages **39, 42** received on **16 October 2003** with the letter of **16 October 2003**

☒ the claims, pages **79** as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **76-78** received on **16 October 2003** with the letter of **16 October 2003**

☒ the drawings, pages **1/14-14/14** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**1-24**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**1-24**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1-24**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 WO 99 00406
D2 Paczkowski N J etal, British Journal of Pharmacology 1999 128 (7) pages 1461-1466

Novelty (N) & Inventive Step (IS) (claims 1-24)

D1 and D2 each discloses cyclic peptides of the same formula as depicted in claim 1 which have the ability to modulate the activity of G protein-coupled receptors. The variable A, B, C, D, E, F and X are defined in different terms from that of instant application and with some exclusions. As a result of the amendments made on 16 October 2003, the claims are directed to cyclic peptides with clearly defined substituents of A, B, C, D, E, F and X. None of the cyclic peptides exemplified has been disclosed by D1 or D2 or obvious to a person skilled in the art. Therefore the subject matter of claims 1-24 is considered novel and inventive and meets the requirements of Articles 33(2) and 33(3) PCT.

Industrial Applicability (IA)

Claims 1-24 are considered to have industrial applicability

"C5a Binding IC50" refers to the concentration of compound required to achieve 50% maximum binding to human PMNs. "C5a Antagonist IC50" refers to the concentration of compound required to achieve 50% antagonism of myeloperoxidase release from C5a-stimulated human PMNs. Boxed regions indicate the location of relative changes between structures. Compound 1 is the lead compound from our previous application PCT/AU98/00490, and is included for purposes of comparison.

Example 3: *Cyclic Antagonists of C5a*

Some examples of these cyclic antagonists and their apparent receptor-binding affinities and antagonist potencies are given in Table 3, in which the single letter code for amino acids is used. "d" indicates the dextro (D) form of an amino acid. "ND" indicates not determined.

Arg Replacements	Lab Code	n	Binding (μM)	Antagonist (nM)
AcF[OPdChaW-**Cit**]	45	3	6.00	690
AcF[OpdChaW-**K**]	47	3	24.15	ND
AcF[OpdChaW-**hArg**]	44	3	1.36	ND

Can = L-canavanine, Cit = Citrulline, hArg=homoarginine

Multiple Replacements	Lab Code	n	Binding (μM)	Antagonist (nM)
AcF[OP-**dPhe-dleu-Nal**-R]	105	3	3.1	ND
AcF[OP-**dPhe-F**R]	62	3	5.2	5,210
AcF[**Dap**OPdChaWRC]	151	3	1.84	100
AcF[OP-**dPhe-1Nal**-R]	63	3	3.1	ND
AcF[OP-**dPhe-Y**-R]	150	3	69.2	ND

1Nal = 1-Naphthylalanine, Dap=2'3-diaminoproprionic acid, dPhe= D-phenylalanine

Example 4: *Pharmacophore Refinement*

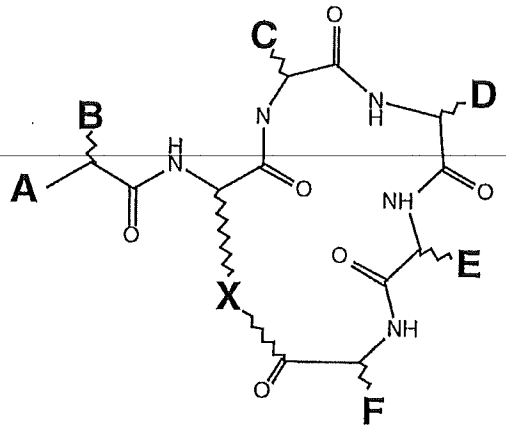
On the basis of the results in Table 2, we can develop a refined pharmacophore for active antagonism of the C5a receptor on human polymorphonuclear leukocytes, as follows:

Position "A" can tolerate a very large number of groups, including H (e.g. compound **17**,**18**), alkyl, aryl, NH_2, NHalkyl, $N(alkyl)_2$, NHaryl, NHacyl (e.g. compounds **1**,**3**,**4**,**5**,**6**,), NHbenzoyl (e.g. compound **2**), OH, Oalkyl, Oaryl, $NHSO_2$alkyl (e.g.compound **10**), $NHSO_2$aryl (e.g. compound **11**), without an adverse effect on activity.

The wide tolerance to substitution at position "A" indicates that there is considerable space in the receptor for appendages to the cyclic peptide scaffold. This position can therefore be used for adding substituents in order to vary the water and lipid solubility of the antagonist, thereby enhancing oral or transdermal absorption of the antagonist. This position

CLAIMS

1. A compound which is an antagonist of a G protein-coupled receptor, which has substantially no agonist activity, and which is a cyclic peptide or peptidomimetic of general formula



where A is H, alkyl, aryl, NH_2, NH-alkyl, $N(alkyl)_2$, NH-aryl, NH-acyl, NH-benzoyl, $NHSO_3$, $NHSO_2$-alkyl, $NHSO_2$-aryl, OH, O-alkyl, or O-aryl;

B is an alkyl, aryl, benzyl, naphthyl or indole group, or is the side chain of L-phenylalanine or L-phenylglycine;

C is the side chain of glycine, alanine, leucine, valine, proline, hydroxyproline, or thioproline;

D is the side chain of D-Leucine, D-homoleucine, D-cyclohexylalanine, D-homocyclohexylalanine, D-valine, D-norleucine, D-homo-norleucine, D-phenylalanine, D-tetrahydroisoquinoline, D-glutamine, D-glutamate, or D-tyrosine;

E is L-1-napthyl or L-3-benzothienyl alanine, or is the side chain of an amino acid selected from the group consisting of L-phenylalanine, L-tryptophan and L-homotryptophan;

F is the side chain of L-arginine, L-homoarginine, L-citrulline, or L-canavanine, or a bioisostere thereof;

X is $-(CH_2)_nNH-$ or $(CH_2)_n-S-$, where n is an integer of from 1 to 4; $-(CH_2)_2O-$; $-(CH_2)_3O-$; $-(CH_2)_3-$; $-(CH_2)_4-$; $-CH_2COCHRNH-$; or $-CH_2-CHCOCHRNH-$, and where R is the side chain of any common or uncommon amino acid,

with the proviso that the compound is not AcF-[OPdChaWR] (compound **1**).

2. A compound according to claim 1, in which n is 2 or 3.

3. A compound according to claim 1 or claim 2, in which A is an acetamide group, an aminomethyl group, or a substituted or unsubstituted sulphonamide group.

4. A compound according to claim 3, in which the substituent on the substituted sulphonamide is an alkyl chain of 1 to 6 carbon atoms, or a phenyl or toluyl group.

5. A compound according to claim 4, in which the alkyl chain is of 1 to 4 carbon atoms.

6. A compound according to any one of claims 1 to 5, in which the compound has antagonist activity against a C5a receptor, a vasopressin receptor or a neurokinin receptor.

7. A compound according to claim 6, in which the compound has antagonist activity against C5aR, and has no C5a agonist activity.

8. A compound according to any one of claims 1 to 7, in which the compound has antagonist activity at sub-micromolar concentrations.

9. A compound according to claim 8, in which the compound has a receptor affinity IC50<25μM, and an antagonist potency IC50<1μM.

10. A compound according to claim 9, selected from the group consisting of compounds **2** to **6**, **10** to **15**, **17**, **19**, **20**, **22**, **25**, **26**, **28**, **30**, **31**, **33** to **37**, **39** to **45**, **47** to **50**, **52** to **58** and **60** to **70**.

11. A compound according to claim 10, in which the compound is compound **33**, compound **60** or compound **45**.

12. A composition comprising a compound according to any one of claims 1 to 11, together with a pharmaceutically-acceptable carrier or excipient.

13. A method of treatment of a pathological condition mediated by a G protein-coupled receptor, comprising the step of administering an effective amount of a compound according to any one of claims 1 to 12 to a mammal in need of such treatment.

14. A method according to claim 13, in which the condition mediated by a G protein-coupled receptor is a condition mediated by a C5a receptor.

15. A method according to claim 14, in which the condition involves overexpression or underregulation of C5a.

16. A method according to claim 15, in which the condition is selected from the group consisting of rheumatoid arthritis, adult respiratory distress syndrome (ARDS), systemic lupus erythematosus, tissue graft rejection, ischaemic heart disease, reperfusion injury, septic shock, gingivitis, fibrosis, atherosclerosis, multiple sclerosis, Alzheimer's disease, asthma, dementias, central nervous system disorders, lung injury, extracorporeal post-dialysis syndrome, and dermal inflammatory disorders such as psoriasis, eczema and contact dermatitis.

17. A method of treatment of reperfusion injury, comprising the step of administering an effective amount of a compound according to any one of claims 1 to 12 or of compound **1** to a mammal in need of such treatment.